# Diabetes Mellitus

Diabetes mellitus (DM) refers to a group of metabolic diseases characterized by hyperglycemia due to insulin resistance or insulin deficiency. It leads to a wide range of complications and, when poorly controlled, contributes to significant morbidity and mortality (see Diabetes Complications chapter). The reported prevalence of diabetes in the US ranges between 7%-15%, depending on race, ethnicity, and sex among adults aged ≥ 18 years.[1] Care of people diagnosed with the disease and its complications accounted for more than 20% of health care dollars spent in the US in 2012.[2]

Type 1 diabetes, accounting for approximately 5%-10% of all cases, occurs after destruction of the insulin-producing beta-cells of the pancreas (usually through an autoimmune process), resulting in a complete insulin deficiency. Most cases present in childhood with polyuria, polydipsia, polyphagia, unexplained weight loss, fatigue, and blurred vision. The condition can also be diagnosed in adults. Type 1 diabetes requires insulin treatment, along with therapeutic lifestyle interventions that are aimed at protecting against damage to blood vessels and organs.

Type 2 diabetes, which accounts for more than 90% of diabetes cases, usually presents in adults after a long, asymptomatic course. About 60%-80% of patients are obese, and prevalence in children is climbing rapidly due to increasing rates of obesity.[3] Type 2 diabetes results from progressive insulin resistance, loss of insulin secretion, and inappropriate hepatic glucose production, resulting in varying degrees of insulin deficiency with subsequent fasting and post-prandial hyperglycemia.[4] Type 2 diabetes is often accompanied by hypertension and lipid abnormalities, which are signs of metabolic syndrome. Although symptoms upon initial presentation tend to be milder in type 2 than in type 1 diabetes, complications are increasingly frequent if metabolic control is poor.

Gestational diabetes mellitus (GDM) has an estimated prevalence of up to about 9%.[5] As its name suggests, GDM is impaired glucose tolerance that first appears during pregnancy. Hormones secreted by the placenta—estrogen, progesterone, growth hormone, corticotrophin-releasing hormone, and prolactin—oppose insulin's function, and the pancreas struggles to produce enough insulin to compensate for the greater caloric intake during pregnancy. Treatment with dietary modification and/or medication (usually insulin) is essential to prevent fetal complications. Although blood glucose levels usually normalize postpartum, women who had GDM have a high risk of developing type 2 diabetes. This risk may be reduced with diet and lifestyle changes.

Other forms of diabetes can result from other disease states or treatments and include:

- Monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY])
- Diseases of the exocrine pancreas (such as cystic fibrosis)
- Drug or chemical-induced diabetes (such as with glucocorticoid use, in treatment of HIV/AIDS or after organ transplant)

## Risk Factors

**Contributors to the risk for developing type 1 diabetes include:**

**Genetic susceptibility**. Close family history of type 1 diabetes significantly increases the risk of development of type 1 in subsequent generations. Multiple genes are associated with the development of type 1 diabetes.[6]

**Exposure to bovine milk proteins**. Consumption of cow's milk in early childhood has been under investigation as a contributing factor, although it has not yet been definitively established.[7]

Fetal or childhood coxsackie virus or enteroviral infections.

Birth weight greater than 4,500 grams.[8]

Respiratory disease of the newborn.[9]

Preeclampsia.[9]

Maternal age greater than 25 years.[9]

ABO incompatibility-induced jaundice.[9]

Oxidative stress from beta-cell exposure to nitric oxide (NO) and oxygen radicals (O 2).[10]

**Risk factors for type 2 diabetes include:**

Adults who are overweight (BMI ≥ 25 kg/m 2 or ≥ 23 kg/m 2 in Asian-Americans) and have any of the following should be screened:[11]

- Physical inactivity.
- First-degree relative with diabetes.
- High-risk race/ethnicity (e.g., African-American, Latino, Native American, Asian-American, Pacific Islander).
- Women who were diagnosed with GDM.
- Hypertension (≥ 140/90 mmHg or on therapy for hypertension).
- HDL cholesterol level < 35 mg/dL (0.90 mmol/L) and/or a triglyceride level > 250 mg/dL (2.82 mmol/L).
- Women with polycystic ovary syndrome.
- A1C ≥ 5.7% (39 mmol/mol), impaired glucose tolerance, or impaired fasting glucose on previous testing.
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans).
- History of cardiovascular disease.

Newly recognized factors that increase risk of type 2 diabetes:

Smoking.[12]

Meat consumption.[13]

Risk factors for GDM are listed below. In addition, individuals of Asian, African, Native American, and Hispanic ancestry have greater prevalence of GDM than non-Hispanic whites.[14] Many of the risk factors for GDM overlap with type 2 diabetes.

Family history of type 2 diabetes in a first-degree relative.[14]

A previous abnormal oral glucose tolerance test.[15]

GDM in prior pregnancy.[14]

Glucocorticoid use during pregnancy.[16]

Polycystic ovarian syndrome.[17]

Advanced maternal age.[14]

Early postpubescent weight gain[14]

Previous child with birth weight greater than 9 pounds.[14]

Previous adverse pregnancy outcome.[15]

Maternal birth weight greater than 9 pounds or less than 6 pounds.[18]

Short stature.[18]

Sedentary lifestyle.[18]

Multiparity.[5]

Excess body weight.[14]

High blood pressure or dyslipidemia.[19]

Smoking.[2]

Other factors, such as chronic sleep loss, may worsen glycemic control among individuals with diabetes.[20]

## Diagnosis

Endocrinopathies, such as Cushing's disease, acromegaly, pheochromocytoma, and hyperthyroidism, may impair glucose tolerance and should be ruled out.

## Type 1 and Type 2 Diabetes

Diabetes and prediabetes are diagnosed based on laboratory values showing blood glucose control.[2] A normal value for fasting plasma glucose is less than 100 mg/dL, and for a 2-hour OGTT is less than 140 mg/dL.

Prediabetes or categories for increased risk for diabetes are:

- A1C 5.7%-6.4%.
- Impaired fasting glucose (IFG): fasting plasma glucose 100 mg/dL to 125 mg/dL.
- Impaired glucose tolerance (IGT) 2-h plasma glucose in the 75-g OGTT 140 mg/dL to 199 mg/dL.

Diabetes is diagnosed based on the following values:

- A1C ≥ 6.5%.
- A fasting plasma glucose concentration ≥126 mg/dL.
- A 75 g, 2-hour oral glucose tolerance test (OGTT) result of 200 mg/dL or greater. If no symptoms of hyperglycemia are present, repeat testing is needed to confirm results.
- A random plasma glucose of 200 mg/dL or greater when classic hyperglycemia symptoms are present.

In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

African-Americans may have higher A1C levels than non-Hispanic whites despite similar fasting and post-prandial blood glucose levels. A1C levels may be also be influenced by the presence of certain hemoglobinopathies and in conditions associated with increased red blood cell turnover, such as pregnancy and hemodialysis. To improve diagnostic specificity, the Veterans Administration/Department of Defense (VA/DoD) recommends that A1C values between 6.5%-7.0% be confirmed with fasting plasma glucose levels.[21]

Type 1 diabetes often presents with ketoacidosis, which is caused by partial or total insulin deficiency and normally requires hospital admission and intensive care. Type 1 diabetes can be confirmed by the identification of islet-cell antibodies or other autoantibodies (e.g., antiglutamic acid dehydrogenase [GAD] or anti-insulin antibodies). However, some patients have no identifiable cause of islet cell destruction.

Patients initially thought to have type 2 diabetes but with autoantibodies most likely have late-onset type 1 diabetes or late-onset autoimmune diabetes. They are unlikely to respond adequately to lifestyle changes and/or oral or injectable antihyperglycemic agents and will likely require insulin.

In all asymptomatic adult patients, testing for type 2 diabetes should begin at age 45, and should be considered at any age for those adults who are overweight and have at least one risk factor for development of diabetes. Tests can

be repeated after 3 years if all results are normal.

## Gestational Diabetes

Screening for GDM is a routine part of prenatal examinations. The current epidemics of poor eating habits and obesity in the US and many other countries put many women of childbearing years at risk for type 2 diabetes. This makes it important to test for undiagnosed type 2 diabetes at the first prenatal visit for those individuals with risk factors (see above) using standard diagnostic criteria.

Screening typically occurs between 24-28 weeks of gestation in women who are at low risk and not previously known to have diabetes. Diagnosis for GDM can be accomplished by either a “one-step” or “two-step” approach:

1. The one-step strategy is conducted at 24-28 weeks gestation with a fasting 75-g OGTT, measuring fasting, 1-hour, and 2-hour plasma glucose levels. Diagnosis of GDM is made when plasma glucose levels exceed the following:

a. Fasting: 92 mg/dL (5.1 mmol/L)
b. 1 h: 180 mg/dL (10.0 mmol/L)
c. 2h: 153 mg/dL (8.5 mmol/L)

2. The two-step strategy involves a 1-hour challenge with a 50-g oral glucose load. A venous serum or plasma glucose greater than or equal to 130 mg/dL, 135 mg/dL, or 140 mg/dL is considered a positive screen, with greater sensitivity at the lower threshold and greater specificity at the higher threshold.[22] If a patient screens positive, she will then proceed to a 3-hour, 100 g OGTT after an 8-hour fast, which is diagnostic for gestational diabetes when glucose values are elevated at 2 different times. The cutoff values for elevated glucose are generally considered to be 95 mg/dL at fasting, 180 mg/dL at 1 hour, 155 mg/dL at 2 hours, and 140 mg/dL at 3 hours.[23]

The one-step approach may significantly increase the number of women diagnosed with GDM, increasing medical costs and “medicalization” of pregnancies. However, there is some evidence that there may be benefits to intervening at lower glucose levels by decreasing large-for-gestational-age births and preeclampsia.

In pregnancy, mildly abnormal glucose levels can lead to fetal complications, which is why fasting serum glucose greater than 92 mg/dL is considered abnormal and treatment is started very early. Treatment should be considered in women with fasting glucose even below the diagnostic values for diabetes due to the increased risk of adverse outcomes, which can occur even with a normal OGTT.[24] Women with GDM should be screened 6-12 weeks postpartum using the OGTT with the normal diagnostic criteria and lifelong screening should be conducted every 3 years, and the nutritional interventions described below should be implemented.

## Treatment

Dietary and lifestyle interventions, including smoking cessation and physical activity, are important for patients with all types of DM (see below). Diabetes self-management education and support is also important, and addresses emotional well-being, psychosocial issues, and education related to disease treatment. Additionally, patients should be routinely screened for depression and anxiety related to their disease.[2]

## A1C Targets

A1C is a fairly accurate gauge of the average blood glucose during the previous 2 to 3 months. A1C levels are often used as an index of the quality of diabetes care, and tight glucose control has long been promoted for both type 1 and type 2 diabetes. However, for people with type 2 diabetes, this clinical focus appears to be misplaced, and may be a distraction from more meaningful clinical markers. Using medication to reduce A1C and blood glucose to near-normal

levels in people with type 2 diabetes has not been shown to improve mortality or prevent clinically relevant complications.[25] ,[26] Furthermore, older adults who achieve an A1C below 7% with medication, with the exception of metformin, are at risk of severe hypoglycemia and increased mortality.[27] ,[28]

This is not to say that glucose control does not matter. Uncontrolled hyperglycemia, or an A1C > 8.5%, may put older patients at risk for dehydration, poor wound healing, urinary tract infections, falls, and hyperosmolar syndrome. This A1C upper limit target is open to interpretation; the guidelines of VA/DoD use a range of > 8%-9% for the most frail patients before treatment with medication is recommended.[21]

Guidelines for medication therapy in type 2 diabetes, such as those of the ADA and VA/DoD, now express a range of appropriate target A1C levels based on patient-specific factors such as life expectancy, comorbidities, and functional limitations, rather than recommending an A1C of < 7 as the target for most patients. To assess life expectancy in complex patients, the Lee Schonberg Index is a validated tool that takes into consideration age, comorbities, behaviors (e.g., smoking) and functional abilities to predict 4- and 10-year mortality risk in adults age 50 and older, which is useful in choosing an A1C target to be achieved with medication, and may be used to recalibrate the target for patients over time. When using lifestyle interventions alone, there is no lower limit A1C target based on any safety consideration.

The A1C test and target are not the most critical clinical target for type 2 diabetes management. As atherosclerotic cardiovascular diseases are the leading cause of morbidity and mortality in people with diabetes, cardiovascular risk factor reduction, such as smoking cessation, antiplatelet therapy, blood pressure control, and lipid reduction, are key targets of care for all people with diabetes.[29]

Some studies show that the relative risk of microvascular complications appears to fall with lower A1C values. However, risk of hypoglycemia in type 1 and hypoglycemia and polypharmacy in type 2 may outweigh the benefit. In type 2 diabetes, the benefits of normalizing A1C on patient-important outcomes (e.g., kidney failure) and on surrogate markers (e.g., albuminuria) with multiple medications used in intensive therapy has recently been found to be overstated in previously published statements, while lifestyle interventions as discussed below may safely lower A1C and offer other beneficial side effects.[30]

For people with type 1 diabetes, intensive management may decrease cardiovascular risk. For those with type 2 diabetes, intensive management with multiple medications does not prevent cardiovascular mortality or stroke, and may actually increase cardiovascular mortality.[31] The ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, which included 10,251 participants, compared intensive treatment (intended to reduce A1C to < 6%) with less-intensive treatment, and showed increased deaths in the intensively treated group, leading to an early termination of this part of the study in 2008.[31]

An A1C goal of < 6.5% to < 7.0% may be reasonable in a patient with no cardiovascular disease, a long life expectancy, or diabetes treated only with lifestyle changes or metformin. A less strict A1C goal, such as < 8% or higher, may be more reasonable for a patient with many comorbidities, a shorter life expectancy, or a history of hypoglycemic episodes. A1C goals should be re-evaluated across the patient's lifespan.

Self-blood glucose monitoring is critical for people with type 1 diabetes and type 2 patients on insulin. It may also be useful when people who have type 2 diabetes need to titrate medications that can cause hypoglycemia or when modifying diet and exercise routines. Self-monitoring has not been shown to have any benefit in patients who are not on insulin or taking medications associated with hypoglycemia. Target blood glucose levels for those who are testing should reflect a range that matches the patient's individualized A1C goal.

## Pharmaceutical Treatment for Type 1 Diabetes

The majority of people with type 1 diabetes should be treated with continuous insulin infusion via a subcutaneous insulin pump, or receive multiple insulin injections per day of both basal and prandial insulin.

**Insulin** is available in several forms that differ in duration of action.

- Long-acting insulins provide basal coverage. Insulin glargine is usually administered daily; insulin detemir may be given once or twice a day.
- NPH is also a basal insulin but has an intermediate length of action and is often administered twice a day.
- Short (regular) or rapid-acting insulin analogs can be administered in boluses before meals to curb postprandial blood glucose elevations and to correct premeal elevations.
- Intermediate insulin is available premixed with short- or rapid-acting insulin when 2 insulin types are required.
- Premixed insulins are primarily used in patients with type 2 diabetes.

**Amylin** is a beta-cell hormone that is co-secreted with insulin. Pramlintide, a synthetic amylin analog, is injected at mealtimes along with fast-acting insulin. It reduces postprandial rises in blood glucose concentrations and suppresses appetite, which may lead to weight loss. Caution should be exercised, however, as severe hypoglycemia may develop.

**Glucagon** injection is an antidote to severe hypoglycemia for an unconscious patient. Patients who are at risk and live with someone who can be trained to use glucagon should be provided with instructions and a prescription.

## Pharmaceutical Treatment of Type 2 Diabetes

Medications for glucose control other than metformin are not recommended for asymptomatic patients of any age with type 2 diabetes because of the lack of benefit and the risk of harm.[27] When the decision is made to treat hyperglycemia, the Diabetes Medication Choice Decision Aid can be used to help decide on an agent that best fits the patient's values and preferences, keeping in mind that there is little meaningful difference between medications in reduction of cardiovascular and all-cause mortality, while there are significant differences in cost, side effects, effect on weight, and contraindications.[32]

## Oral Agents

**Biguanides**. Metformin is recommended as the first-line agent, as it provides effective glycemic control, does not promote weight gain, is usually well tolerated, and is affordable for many patients. It decreases hepatic gluconeogenesis and increases insulin sensitivity. Metformin modestly reduces the risk of cardiovascular events, irrespective of its impact on glycemia, and may also reduce mortality because of an anticancer effect.[33] It is contraindicated in heart failure, renal insufficiency, liver disease, excessive alcohol intake, serious infection and illness, and other disease processes. Gastrointestinal disturbances are common but usually abate over time. Chronic use of metformin results in vitamin B12 deficiency in 30% of patients, and may be misdiagnosed as diabetic neuropathy.[34]

None of the agents listed below, when used to achieve tight glycemic control, have shown an absolute benefit on patient-centered outcomes, such as prevention of kidney failure, loss of eyesight, amputation, or mortality.[30] The descriptions below provide a brief overview; consult the prescribing information for more comprehensive information.

Sulfonylureas. Glipizide, glyburide, and glimepiride are the most commonly used medications in the class of sulfonylureas. These medications work by stimulating the pancreatic beta-cells to release insulin. Glipizide is shorter-acting and may be preferable for geriatric patients or those with renal or hepatic insufficiency. Sulfonylureas may cause hypoglycemia and weight gain, as well as dose-related gastrointestinal effects such as nausea, diarrhea, and constipation. They often cease to be effective within a few years.

**Thiazolidinediones**. Pioglitazone and rosiglitazone increase insulin sensitivity in peripheral tissues like muscle, fat, and the liver decrease glucose production, and may also increase insulin secretion. These medications are generally well-tolerated by patients and do not cause hypoglycemia as monotherapy. They are contraindicated in heart failure. Weight gain, fluid retention, and hepatic injury are possible side effects, especially when combined with insulin, and liver enzymes should be routinely monitored. Reports have raised concerns about cardiac risks of rosiglitazone and a

possible increased risk of myocardial infarction and heart failure. However, in 2013 the US Food and Drug Administration removed its prescribing and dispensing restrictions concluding that rosiglitazone does not increase the risk of myocardial infarction compared with other diabetes medications, including metformin and sulfonylureas.[35] Pioglitazone should not be used in patients with active bladder cancer and may raise the risk of developing bladder cancer. TZDs may cause macular edema and increased incidence of bone fractures.

**Meglitinides**. Nateglinide and repaglinide stimulate insulin secretion but are shorter-acting than sulfonylureas and must be taken before meals. Dose reduction is required for hepatic or renal impairment. They may cause hypoglycemia, weight gain, and flu-like symptoms.

**Alpha-glucosidase inhibitors**. Acarbose and miglitol inhibit the conversion of carbohydrates to monosaccharides, slow the absorption of glucose, and lower postprandial glucose values. They need to be taken at the beginning of a meal. Flatulence, abdominal cramping, and diarrhea are common side effects and may limit compliance.

**DPP-IV inhibitors**. Alogliptin, saxagliptin, sitagliptin, and vildagliptin inhibit the enzyme that degrades endogenous incretin hormones. This results in increased glucose-dependent insulin secretion, decreased glucagon secretion, and delayed gastric emptying. Sitagliptin and saxagliptin must be given at a lower dose for those with renal insufficiency. These agents are expensive and are most effective in drug-naïve patients.

**SGLT2 inhibitors**. Canagliflozin, dapagliflozin, and empagliflozin decrease the reabsorption of glucose in the kidneys, increasing glucose in the urine, which can result in urinary tract and genital mycotic infections. They may also cause hypotension and should be used cautiously with antihypertensive medications, especially diuretics, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers. These agents increase urination. They may also increase LDL-cholesterol concentrations and, when used in combination with insulin/insulin secretagogues, may cause hypoglycemia. Renal and liver function and potassium levels should be monitored. Canagliflozin may reduce bone mineral density and increase fracture risk.[36] These agents are expensive.

## Noninsulin Injectables

**GLP-1 analogues**. These injectable synthetics are used to increase mealtime insulin secretion in type 2 diabetics, usually as an add-on to metformin or an insulin secretagogue. They vary from twice daily (taken 30-60 minutes before meals) (exenatide, liraglutide, and lixisenatide), to once daily (liraglutide), and once a week (albiglutide, dulaglutide, and exenatide extended-release). They are less likely to cause hypoglycemia, compared with insulin or insulin secretagogues, and may promote satiety, leading to decreased appetite and modest weight loss. Nausea, vomiting, and diarrhea are common side effects, and can lead to renal impairment. Reduced doses should be used in patients with renal impairment. These agents are expensive and carry a risk of thyroid tumors and pancreatitis, which may be fatal.

**Amylin analog**. Pramlintide (described above) may also be used in type 2 diabetes.

## Insulin

The insulin formulations described above for type 1 diabetes are appropriate for use in type 2 when a patient is symptomatic, unable or unwilling to make lifestyle modifications, unable to take metformin, or already on 2 grams of metformin daily, and with an ability to safely inject insulin, monitor blood glucose levels, and recognize and treat hypoglycemia. There is no evidence of benefit for starting insulin therapy early in the course of type 2 diabetes. In several trials (ACCORD, VADT, and NICE-SUGAR) type 2 diabetes patients who were prescribed insulin to achieve an A1C ≤ 7% were eventually found to have an increased incidence of severe hyperglycemia and cardiovascular mortality. Apart from its use for symptom control (ideally for short periods), there is no benefit to insulin use in people with type 2 diabetes; it may reduce quality of life.[33] When insulin is required in type 2 diabetes, the best regimen is the one that (1) results in adequate blood glucose control with a dosing schedule that is acceptable to the patient and (2) causes the fewest episodes of hypoglycemia. Clinicians should avoid the common practice of overtreatment of

type 2 diabetes with medications, and should de-intensify insulin and other pharmaceutical interventions through dose reduction or discontinuation. In some cases, insulin and other agents can be withdrawn, with blood glucose levels maintained through lifestyle interventions alone.

A caveat to this approach applies to patients with presumed type 2 diabetes and autoantibodies, who are less likely to respond to the oral agents. Such patients may require insulin therapy (see type 1 diabetes) and are at increased risk of ketoacidosis.

## Treatment of Gestational Diabetes

Nutrition therapy is the first-line treatment for GDM. When adequate glycemic control is not attained through nutrition modification, insulin should be considered.

Insulin is the best-studied pharmaceutical agent for GDM, and it is the only recommended treatment in the US. Oral anti-hyperglycemics are not approved for the treatment of GDM by the FDA; however, the American Diabetes Association and the American College of Obstetricians and Gynecologists both support the use of oral therapy (metformin and glyburide) during pregnancy. Dietary interventions are discussed in detail under Nutritional Considerations below.

## Role of Physical Activity

A sedentary lifestyle is associated with increased risk for impaired glucose tolerance and diabetes.[37] Exercise[38] and diet-exercise programs that produce weight loss significantly reduce the risk for type 2 diabetes.[39] ,[40] The American Diabetes Association recommends at least 150 minutes per week of aerobic exercise, divided among at least 3 days per week, with at most 2 consecutive days of rest. Resistance training should be performed a minimum of twice weekly.[11]

Exercise alone has little or no effect on body weight.[41] However, in persons with established diabetes, exercise reduces blood glucose and plasma lipid concentrations[42] and improves insulin sensitivity, independent of weight loss. Exercise also reduces cardiovascular complications of diabetes, including high blood pressure, left ventricular diastolic function, arterial stiffness, systemic inflammation, and left ventricular mass.[43]

Women who either have or are at risk for gestational diabetes can also benefit from exercise. Independent of body mass index, women who regularly engage in moderate exercise (e.g., brisk walking) are at reduced risk of GDM.[44] In women with GDM, exercise has been found to be a useful strategy for helping to maintain blood glucose within the normal range and to control blood glucose without the use of insulin.[45]

Medications, especially insulin acting during the time of the activity, may need to be adjusted or carbohydrate intake increased on days when exercise occurs.

Certain pharmaceuticals, such as beta-blockers, thiazides, oral contraceptives, niacin, and glucocorticoids, can impair glucose tolerance and raise A1C levels.

## Nutritional Considerations

### Prevention: Type 1 Diabetes

Compared with a stable and relatively low incidence of type 2 diabetes in the first half of the 20th century, incidence rose in the latter half of the century and is now increasing by 3% per year,[46] a rate faster than can be explained by genetic factors.[47] Putative explanations include changes in infant diets, particularly the lack of breastfeeding and increased exposure to cow's milk, the role of hygiene, differences in gut microbiota and abnormalities in gut

permeability, and a high maternal body mass index (BMI) during pregnancy.[48] The following considerations have emerged as potentially important candidates for preventive strategies, although none has been definitively established:

**Breastfeeding**. In a pooled analysis of 43 observational studies involving nearly 10,000 patients, exclusive breastfeeding for greater than two weeks and more than three months was associated with a 25% and 13% lower risk for type 1 diabetes, respectively.[49] Longer duration of breastfeeding may reduce risk for type 1 diabetes, presumably by prolonging avoidance of exposure to cow's milk proteins or other antigens, increasing protection against infections, enhancing the infant's immune responses, and increasing beta-cell proliferation.[50] An autoimmune mechanism may also be involved (see below). Although breastfeeding is the best choice for infant feeding, ethical and practical difficulties have prevented controlled trials of its effect on diabetes risk.

**Avoidance of early introduction of cow's milk**. Human studies show that cow's milk intake in childhood is associated with both an increased risk for development of islet cell autoantibodies and type 1 diabetes.[51]

The associations between these variables are thought to be attributable to molecular mimicry, breakdown of tolerance, or a lack of certain cytokines and growth factors.[31] Another potentially causative agent is *Mycobacterium avium* subspecies *paratuberculosis* (MAP), which has been detected in retail milk and cheese.[52] Although it has not yet been proven conclusively that cow's milk is a trigger for type 1 diabetes, the American Academy of Pediatrics concluded that avoiding early exposure to cow's milk may reduce the risk.[53]

The question of whether the early ingestion of intact foreign proteins contained in cow's milk may increase type 1 diabetes risk may be answered in part by the Trial to Reduce Type 1 Diabetes in the Genetically at Risk (TRIGR) study. This international effort will test the hypothesis that weaning infants to an extensively hydrolyzed formula instead of cow's milk may delay or prevent the onset of type 1 diabetes in genetically susceptible children.[54] Although the results of this study are pending, TRIGR investigators have reported that the highest levels of insulin antibodies were found in infants fed exclusively cow's milk formula, compared with those who received both breast milk and cow's milk or breast milk alone.[55] A smaller study with a similar design found that this intervention resulted in a significant protection from positivity for islet cell antibodies.[7]

**Avoiding early introduction of gluten-containing foods**. A high degree of concordance between type 1 diabetes and celiac disease has been observed.[56] In epidemiologic studies, supplementing infant diets with gluten-containing foods before 3 months of age or later than 6 months is associated with increased risk for developing islet cell autoantibodies and type 1 diabetes.[57] In some children, both early (before 3 months) and late (after 7 months) introduction of cereals was associated with increased risk of islet autoimmunity, suggesting that there may be a window of exposure to cereals, outside which initial exposure increases islet autoimmunity risk in genetically susceptible children.[58]

Researchers are seeking ways to prevent autoimmune attacks of pancreatic beta-cells, with the goal of reducing the risk for developing insulin-dependent diabetes. So far, evidence suggests that the following dietary factors may protect against the development of type 1 diabetes: breastfeeding rather than exposure to dairy-based formulas, probiotic supplementation,[59] and vitamin D supplementation during both pregnancy and the infant's first year of life.[60] All of these actions are capable of modulating the production of proinflammatory cytokines that are known to be involved in the pathogenesis of type 1 diabetes.[61]

## Prevention: Type 2 Diabetes

Although type 2 diabetes has a genetic component, diet and lifestyle significantly affect the likelihood that the disease will manifest and also influence its course after diagnosis. The risk for type 2 and gestational diabetes can be decreased by avoiding overweight and by following specific dietary and lifestyle practices. Notably, the Diabetes Prevention Program demonstrated that dietary changes designed to reduce body weight, combined with regular exercise, can significantly reduce the risk for type 2 diabetes. Risk reduction was 58% in the group that combined diet and exercise compared with placebo. Those on drug (metformin) treatment had a 31% reduction. In individuals age

60 and older, the risk reduction was 71% with diet and exercise.[43]

Individuals in Asia and Africa who follow traditional diets low in animal fat and high in complex carbohydrates and who remain physically active have a far lower incidence of diabetes than those who follow a Western diet and activity pattern.[62] A number of reviews have concluded that plant-based dietary patterns rich in fruits, vegetables, legumes, and nuts are the most effective approaches to the prevention and management of type 2 diabetes.[63] ,[64] ,[65] Vegetarians also have a lower prevalence of diabetes than their omnivorous counterparts.[13],[66] ,[67]

In a cohort of more than 60,000 participants in the Adventist Health Study 2, the vegan group had the lowest incidence of type 2 diabetes: 2.9% compared to 7.6% in the nonvegetarian group.[68] More than 6,000 adults ages 50 and over from NHANES III were followed for 18 years. When categorized for animal protein intake, those with the highest intake were associated with a 73-fold increase of diabetes mortality, a moderate intake was associated with a 23-fold increase, while vegetable protein was not associated with an increase in risk.[69] A systematic review and meta-analysis of randomized controlled trials revealed that replacing animal protein with plant protein improves glycemic control in individuals with diabetes.[70] A meta-analysis of more than 50,000 nondiabetic whites found that regardless of genetic risk of diabetes, meat consumption was associated with higher fasting glucose and insulin concentrations.[71]

These results are probably due to several factors. Intake of saturated fat reduces both insulin secretion and insulin receptor activity[72] and is associated with impaired glucose tolerance, insulin resistance, gestational diabetes, and type 2 diabetes.[73]

It has been suggested that meat consumption should be identified as a risk factor for type 2 diabetes, as several possible mechanisms link meat consumption to diabetes risk.[13]Higher meat consumption is associated with an increase in body weight, as meat is typically higher in calories when compared with plant-based foods. [74],[75] Meat intake is also associated with inflammation, a greater deposition of fat in the visceral tissue, and an unhelpful accumulation of stored iron. [76] Nitrates in processed meats has also been associated with diabetes.[76] Advanced glycation end products found in meat products may contribute to the development of diabetes and microvascular complications.[76]Meat increases plasma levels of L-carnitine, which is metabolized to trimethylamine N-oxide, which increases the risk of cardiovascular disease, a significant risk factor of diabetes.[77]

In contrast, diets richer in plant-based foods—fruits, vegetables, whole grains, and beans—result in lower postprandial glucose and are associated with a significantly lower risk for type 2 diabetes.[78],[79] ,[80] High-fiber diets often contain micronutrients important in glucose tolerance, including magnesium and vitamin K. A study of more than 127,000 men and women found that consuming the highest amount of magnesium was associated with a roughly 35% lower risk for development of type 2 diabetes compared with consuming the least amount.[81] ,[82] ,[83] Conversely, a meta-analysis of prospective and cross-sectional studies revealed that a high intake of heme iron (e.g., in meat) is associated with a significantly increased risk for type 2 diabetes.[76]

Recent reviews have concluded that, as in type 2 diabetes, diets to prevent and manage GDM should be high in complex carbohydrates, fiber, fruits, vegetables, and whole grains.[84] ,[85]

Many patients with diabetes incorrectly assume that they should avoid carbohydrates in order to control blood sugar. However, a systematic review and meta-analysis found that individuals most strictly adhering to such diets had a roughly 30% greater risk for all-cause mortality compared with those who were least adherent.[86]

## Nutritional Management

Nutrition therapy may be beneficial in both type 1 and type 2 diabetes.

The goals of nutrition therapy in diabetes management include control of glucose to near-normal levels, normalization of serum lipids and blood pressure, and attainment of a healthy weight. Adherence to a healthful diet, regular exercise, and use of medications when necessary may achieve these goals and help minimize the risk of complications.

The American Diabetes Association (ADA) recommends an individualized approach to medical nutrition therapy, promoting nutrient-dense foods in appropriate portion sizes to achieve therapeutic goals (body weight, A1C, BP, lipids, and prevention of complications). ADA recommends carbohydrate counting for people with type 1 diabetes and those with type 2 on flexible insulin dosing. For those on fixed insulin dosing, a consistent intake of carbohydrate is recommended. The ADA does not recommend any specific macronutrient distribution or eating pattern, but does encourage the intake of carbohydrate foods such as whole grains, vegetables, fruits, legumes, and dairy products; emphasizing foods high in fiber and low in glycemic load; discouraging the consumption of foods and beverages high in sugar, specifically sugar-sweetened beverages. In overweight or obese individuals, ADA recommends reducing caloric consumption by 500-750 kcal/day (or 1,200-1,500 kcal for women and 1,500-1,800 kcal/day for men) to achieve a weight loss of 5% to < 7%. ADA also recommends that adults who consume alcohol do so in moderation, limiting alcohol to ≤ 1 drink/day for women and ≤ 2 drinks/day for men, and limiting sodium consumption to < 2,300 mg/day.[87]

The American Association of Clinical Endocrinologists and the American College of Endocrinology encourage a plant-based dietary pattern for weight attainment and maintenance.[88]

Although the most effective types of diets (including low glycemic index, Mediterranean, and vegan patterns) significantly improve glycemic control compared with usual diets,[89] there are reasons to believe that plant-based diets are superior not only for preventing diabetes but for managing its complications.

A low-fat, plant-based diet influences nutrient intake and body composition in several ways that may, in turn, affect insulin sensitivity: first, because such diets are low in fat and high in fiber, they typically cause covert reductions in energy density and energy intake, which are not fully compensated for by increased food intak e.[90] ,[91] ,[92] The addition of 14 g of dietary fiber per day is associated with a 10% decrease in energy intake.[93] As a result, low-fat, vegan diets are associated with significant weight loss,[94] an important effect given that increased body fat, especially visceral fat, is associated with insulin resistance.[95]

Carbohydrate type may influence glucose control. A review of 5 studies of individuals with type 1 or type 2 diabetes showed that diets with lower glycemic indices significantly reduced A1C concentrations.[96] Diets that provide carbohydrates in unrefined form or as low glycemic index foods are more effective than low carbohydrate diets in managing gestational diabetes.[85]

Furthermore, diets richer in fiber tend to produce lower postprandial blood glucose concentrations compared with fiber-depleted diets, and high-fiber diets have been shown to improve glycemic control in individuals with type 2 diabetes.[97] Because vegan diets consist solely of plant-derived foods, they are typically high in fiber, compared with nonvegan diets.[98]

Finally, limited evidence suggests that elevated body iron stores are associated with insulin resistance, while reductions in iron stores by any means (e.g., dietary alterations or phlebotomy) increase insulin sensitivity. A vegan diet provides iron in its non-heme form, which is somewhat less absorbable than heme iron. A study comparing 30 ovolactovegetarians and 30 meat eaters, all of whom were healthy and had BMIs < 23 kg/m 2, showed that the vegetarians had adequate, but lower, body iron stores compared with the meat eaters: serum ferritin concentration 35 $\mu$ g/L (95% CI, 21-49) versus 72 $\mu$ g/L (95% CI, 45-100). The vegetarians also demonstrated less insulin resistance than the meat eaters: steady-state plasma glucose concentration 4.1 mmol/L (95% CI, 3.5-5.0) versus 6.9 mmol/L (95% CI, 5.2-7.5).[93]

Similar dietary changes are helpful for patients with type 1 diabetes and are badly needed, given a review of studies that examined food intake in children with type 1 diabetes and found higher intakes of saturated fat and lower intake of fruits, vegetables, and fiber compared with their nondiabetic peers.[99] A high-fiber diet results in lower insulin requirements and improved management of blood glucose and lipids.[100] The ability of plant-based diets to reduce cardiovascular risk factors is likely to be important in type 1 diabetes as well.

Because lifestyle change must be permanent in diabetes, as in many other medical conditions, adherence is a clinical challenge. Researchers have long lamented the poor adherence achieved with typical diets for diabetes.[101] A potential weakness of such diets is that they require portion size limits for overweight persons, and limits on saturated

fat intake are based on these limited energy intakes. As a result, individuals who exceed their prescribed energy intake limits with outsized portions can easily exceed recommended limits on saturated fat.

In this respect, vegan diets may present a clinical advantage. Because they include no animal fat, variations in food quantity are less likely to result in substantial increases in saturated fat intake. While vegetarian or vegan diets may sound restrictive, their acceptability in clinical studies is similar to that of seemingly more moderate therapeutic diets.[102] ,[103] ,[104] ,[105] Because vegan diets are based on the elimination of certain foods, they require no specified limits on portions, calories, or carbohydrates and may be simpler to understand than regimens that limit quantities of certain foods without proscribing any. While individuals vary in their adherence to therapeutic diets, studies suggest that the more far-reaching the diet changes that are recommended by clinicians, the more changes patients actually make.[106]

Alcohol has mixed effects, and has a U-shaped associated with diabetes.[53]

A recent 2-year randomized controlled clinical trial in abstinent patients with type 2 diabetes given 5 ounces of red or white wine per day revealed that only slow ethanol metabolizers significantly benefited from the effect of both wines on glycemic control with reductions in fasting glucose, insulin resistance, and hemoglobin A1C, compared with fast ethanol metabolizers.[107] Also, alcohol consumption carries significant risks. For individuals treated with insulin or sulfonylureas, alcohol can increase the risk of hypoglycemia. In addition to potentially increasing breast cancer risk and potentially causing hazardous interactions with medications, alcoholic beverages consumed at mealtime can impair a patient's resolve to follow a healthful diet. Therefore, a physician should discuss alcohol consumption with individuals at risk for type 2 diabetes.

## Dietary Supplements in Type 2 Diabetes

Several supplements have been investigated for their role in diabetes management, notably chromium and certain botanicals:

**Chromium**. The role of chromium as an insulin co-factor was discovered relatively recently.[108] In 1977, Canadian researchers described the case of a woman in her mid-30s who received nutrition parenterally as a result of prior intestinal surgery. Gradually worsening weight loss, hyperglycemia, and neuropathic symptoms led her doctors to institute treatment with increasing insulin doses. Eventually, the addition of chromium to her feeding regimen permitted discontinuance of insulin and marked symptomatic improvement.[109]

Until recently, the mechanism whereby chromium may improve indices of glucose metabolism was unknown. Current evidence indicates that this mineral works by increasing the presence of the main insulin-responsive glucose transporter (GLUT4) to the plasma membrane[110] and by enhancing tyrosine phosphorylation of the insulin receptor.[111]

Dietary Reference Intakes (DRI) for micronutrients do not take into account the increased need for certain nutrients caused by certain diseases, including diabetes. Plasma levels of chromium have been found to be 25%-30% lower in diabetic persons with mild or severe hypoglycemia than in euglycemic individuals.[112]

Although correcting chromium deficiency improves blood glucose control, it is not yet clear that additional chromium helps. Meta-analyses have shown mixed results, with some concluding that chromium supplementation did not improve fasting plasma glucose levels[113] and others concluding that when taken either by itself or with vitamins C, E, or biotin, chromium significantly improves glycemic control, while chromium alone significantly reduces triglycerides and increased HDL-C levels.[114]

According to the Food and Nutrition Board of the Institute of Medicine, the safe and adequate daily intakes of chromium for adults 19-50 years of age are 35 mcg for men and 25 mcg for women. For people over 50, the numbers are 30 mcg for men and 20 mcg for women.

**Magnesium**. A recent review concluded that magnesium supplementation is warranted for patients who are

magnesium-depleted.[115] Magnesium increases insulin sensitivity and may also augment insulin secretion. Higher magnesium intakes can be achieved through diet by consuming whole grains (e.g., brown rice, barley, and oats) and green vegetables, such as spinach and Swiss chard, and certain kinds of legumes.

**Botanicals**. The role of certain botanicals for patients with type 2 diabetes is under investigation. Metformin, for example, was developed from *Galega officinalis* (French lilac).[116] Many botanical products, including *Ipomoea batatas* (caiapo), *Trigonella foenum-graecum* (fenugreek), *Momordica charantia* (bitter melon), *Gymnema sylvestre* (gurmar), *Opuntia fuliginosa* (prickly pear cactus), and *Opuntia streptacantha* (nopal) have been shown to be effective for lowering blood glucose in controlled clinical trials with small numbers of patients, and further evidence of their efficacy is pending.[115] Clinical trials of certain botanicals have suffered from a lack of standardization of active ingredients,[117] and long-term safety and efficacy have not been established. Patients should be aware that, even in trials showing improvement in glycemic control, glucose levels typically do not return to normal, so medications may still be required. The botanical products proven most effective thus far for diabetes include cinnamon, ginseng, and resveratrol.

An updated systematic review and meta-analysis of randomized controlled clinical trials found that cinnamon use in amounts between 120 mg/d and 6 g/d for 4-18 weeks was associated with statistically significant decreases in fasting plasma glucose, total cholesterol, LDL, and triglyceride levels. However, no significant effect on hemoglobin A1C was found. To be used safely, varieties of cinnamon including *Cinnamomum zeylanicum* (Ceylon cinnamon) should be used, and *Cinnamomum cassia* (Chinese cinnamon) avoided, due to its high coumarin content.[118]

A systematic review and meta-analysis of randomized controlled trials found that *panax* ginseng significantly reduces fasting blood glucose and A1C.[119] Its effects have been attributed to modulation of glucose absorption, insulin secretion and binding, glucose transport, and glucose disposal.[120] A meta-analysis of 11 controlled trials found that resveratrol supplements significantly reduced fasting glucose, A1C, insulin, and insulin resistance,[121] and a systematic review found that when used as an adjunct to medication, resveratrol supplements significantly lowered A1C and systolic blood pressure.[122] Resveratrol is thought to reduce blood glucose by a number of diverse mechanisms, including the AMPK/SIRT1/PGC-1α pathway.[123]

## Orders

Lifestyle changes aim not only to improve blood glucose control, but also to prevent and treat complications, offering important health advantages that medications alone may not offer.

A low-fat, nondairy vegetarian (vegan) diet is helpful for patients with patients with diabetes, improving their body weight, glycemic control, plasma lipids, and blood pressure and improving indices of neuropathy. An emphasis on l ow–glycemic index foods provides additional benefits. A diet following recent ADA guidelines may also be considered, particularly for those who have already had good success with these approaches.

Pregnant patients s hould work closely with a dietitian to ensure adequate nutrient intake.

Vitamin B12 supplements are important for anyone following a plant-based diet, but are particularly so for patients taking metformin and those over age 50.

For some, self-monitoring of blood glucose and use of appropriate oral medication and/or insulin are also recommended.

Nutrition consultation is essential for advising patient in above dietary recommendations and arranging follow-up.

Exercise prescription, individualized.

## What to Tell the Family

The risk of developing type 2 and gestational diabetes can be reduced through healthful dietary habits and regular physical activity.

These measures are important even in individuals who are not overweight. In established disease, the risk of complications is reduced through the healthful dietary habits, particularly a lowe-fat plant-based (vegan) dietary pattern emphasizing low-glycemic index foods. Exercise, both aerobic and resistance training, are key parts of diabetes management. For some, selfmonitoring of blood glucose and use of appropriate oral medication and/or insulin are also recommended. Family members can help prevent and more effectively manage diabetes by following similar dietary recommendations.

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